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UTILITY OF SERUM PROTEIN-BOUND NEUTRAL HEXOSES AND L-FUCOSE FOR ESTIMATION OF MALIGNANT TUMOR EXTENSION AND EVALUATION OF EFFICACY OF THERAPY

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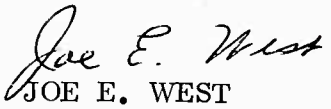

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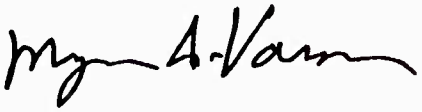

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TABLE OF CONTENTS

LIST OF FIGURES

TABLE

FOREWORD
(Nontechnical summary)

All of the blood serum proteins except albumin have carbohydrate (sugar) molecules attached as side chains to the protein core. The serum concentrations of various of these bound carbohydrates have been found to increase markedly in cancer which had spread to multiple locations in the body (metastatic), but similar responses in other diseases have precluded their use as laboratory aids for differential diagnosis.

One class of these protein-bound carbohydrates, the neutral hexoses, has been reported to increase in certain diseases roughly proportionate to the severity of the condition, suggesting that, in cancer, they may vary directly with the extent of spread of the tumor in a given patient. Serum levels of another, the protein-bound fucose, appear to be quite sensitive for differentiation of localized from disseminated tumors and have been reported to remain within normal limits in some diseases in which the neutral hexoses are elevated.

Unfortunately, in a large majority of the reported work, the data were treated statistically rather than being related to the patients as individuals. Therefore, they could only be applied as distributions of values in groupings of patients with similar diseases, and specific exceptions to the rule could not be identified or reconciled.

This report examines alterations in the serum protein-bound neutral hexoses and fucose and their relationship to one another in a variety of disease states, with especial emphasis on their utility in clinical evaluation of cancer.

The levels of these carbohydrates, expressed as the amount of bound neutral hexoses or fucose per unit weight of serum protein, were examined in 109 cancer

patients and 61 individuals with diagnoses other than malignancy. The results indicated that, while these two parameters were not by themselves sufficient for differential diagnostic application, excellent correlation for presurgical estimation of tumor extension or activity and postsurgical evaluation of efficacy of treatment was achieved.

The uncertainty involved in clinical and surgical assessment of localized versus disseminated disease, as well as clinical judgment of the stability of tumor processes under therapy is emphasized. Thus, in the former, a positive finding of metastatic involvement is incontestable, while failure to demonstrate such involvement is not conclusive. Similarly, relegation of abnormal values in patients with clinical assessment of "quiescent" tumors or diagnoses of "nonmalignant disease" to the category of "false positives" is, of necessity, done by the very means the procedures under development and testing are intended to complement. Indeed, six patients who had been hospitalized with diagnoses other than malignancy, exhibited abnormal values and were classified as false positives. Subsequent work-up, however, demonstrated either an occult tumor or concurrent metastatic disease not associated with the chief complaint for which they had been admitted.

Elimination of the above restrictions, that is, considering only those cases in which evidence of dissemination of disease was positive or unsatisfactory response to therapy was unequivocal, the correlation was 94.4 percent and 100 percent, respectively.

ABSTRACT

A method is employed which permits correction for the influence of the neutral hexoses galactose and mannose on the apparent concentration of protein-bound L-fucose as estimated by the Dische-Shettles CyR3 reaction. The values thus obtained, together with the serum concentrations of neutral hexoses, were evaluated in a series of patients, 109 of whom had confirmed diagnoses of cancer. While these two parameters, protein-bound neutral hexoses and protein-bound fucose, were not by themselves sufficient for differential diagnostic application, excellent correlation for presurgical estimation of tumor extension or activity and postsurgical evaluation of efficacy of treatment was achieved.

I. INTRODUCTION

The serum protein-bound carbohydrates have been examined by numerous investigators as possible sources of criteria for differentially diagnosing malignant neoplasia from nonmalignant disease states. As a result, a large volume of literature has accumulated over the last quarter century to which comprehensive reviews to 1969 are available.[1,17]

Despite an underlying consistency in the reported investigations, that significant deviations from the norm were uniformly demonstrated in malignant neoplasia with metastases, similar responses in the serum concentrations of the various protein-bound carbohydrates in a number of other diseases have precluded their use as objective laboratory aids for differential diagnosis.

Thus, the protein-bound neutral hexoses galactose and mannose have been shown to increase in a number of infectious, inflammatory, and idiopathic diseases as well as in malignancy.[6,11,12,19]

In addition to cancer, the methylpentose L-fucose has also been reported to be elevated in such nonneoplastic diseases as tuberculosis, subacute bacterial endocarditis, parenchymatous liver disease, rheumatoid arthritis, chronic evolutive polyarthritis, diabetes complicated by vascular disease, traumatic injuries, and acute hemorrhage.[5,7,10,18,19]

The lack of specificity of these bound carbohydrates for cancer diagnostic screening procedures, however, does not preclude promise for their utility in the area of management of patients with established diagnoses of malignant neoplasia.

Thus, by combining the evidence, that elevation of the protein-bound neutral hexose concentrations in the serum of such patients appeared to be indicative of dissemination of their disease,[7,12] with the additional finding that, by this parameter, one is able to differentiate active from inactive phases of rheumatoid arthritis, rheumatic fever, and gout, and the degree of advancement of pulmonary tuberculosis,[11] one may hypothesize that these carbohydrates may vary directly with the extent of metastatic involvement.

Protein-bound fucose also appears to be quite sensitive for differentiation of localized from disseminated tumors, especially when expressed as a ratio of bound fucose to protein[3,8,10] and has been reported to maintain normal levels in some nonmalignant processes in which the neutral hexoses are elevated.[10,19]

A potential of this latter parameter as a laboratory aid for differential diagnosis is exemplified by the finding that individuals taking oral contraceptives or with uncomplicated pregnancies maintained normal levels of fucose to protein,[16] whereas patients with invasive gynecologic cancer exhibited elevated ratios.[3]

Unfortunately, in a large majority of the reported work, the data were reduced to statistical parameters rather than being related to the patients as individuals. That the latter procedure promises to be of distinct value as an aid to the presurgical clinical evaluation of cancer patients is well illustrated by two examples.

Rosato et al.,[9] found that, in 31 cases of breast cancer, only one of the seven patients whose fucose to protein ratios were below their delimiting value of 3.5×10^{-3} mg fucose per mg protein demonstrated histological evidence of metastasis. All 24 individuals with ratios above that value had disseminated disease.

Saifer and Weintraub[10] dealt with a variety of tumor types and found less discrimination between early (localized?) and advanced disease. Thus, while all 32 cases of advanced cancer had fucose to protein ratios equal to (5 cases) or higher than (27 cases) the upper limit of their normal value, one-half of the 18 patients with early cancer were also elevated. This could imply that the site or histological type of the tumor may play a role in discrimination.

This report examines alterations in the serum protein-bound neutral hexoses and L-fucose and their relationship to one another in a variety of disease states, with especial emphasis on their utility in clinical evaluation of malignant neoplasia.

II. MATERIALS AND METHODS

Three hundred and twenty-four blood samples were obtained from 316 individuals, 107 of whom were volunteer controls: 66 males and 41 females, ranging from 19 to 62 years of age, with no clinical evidence of disease. Sera from 39 individuals with normal, uncomplicated pregnancies were obtained from the U. S. Naval Hospital, Bethesda, Maryland: 11 in the first trimester, 12 in the second, and 16 in the third. The remaining 170 individuals were either inpatients or outpatients of that hospital. Of these, 109 had primary diagnoses of malignancy; the remaining 61 were afflicted with a variety of other disease states. All were in the process of diagnostic work-up or were in various stages of treatment.

Fasting blood samples (5 ml) were taken by venipuncture. The blood was allowed to clot; the serum was recovered by centrifugation, divided into aliquots so each specimen needed to be thawed only once, and stored in an ultralow temperature freezer (-85^{o}C) until analyzed.

Total protein was estimated by the biuret method, using a commercial, stabilized reagent (Hycel No. 201A, Hycel, Inc., Houston, Texas). Commercially prepared, crystallized human serum albumin (Dade Division, American Hospital Supply Corporation, Miami, Florida) was used as a standard.

Protein-bound fucose concentration (as 6-deoxy-L-galactose) was determined by Winzler's modification[19] of the CyR3 method of Dische and Shettles.[4] The net optical density (396 nm - 430 nm) was measured in a Beckman Acta II spectrophotometer (Beckman Instruments, Inc., Fullerton, California) which gives wavelength accuracy of ±0.5 nm. These raw values were corrected for the influence of nonfucose carbohydrate moieties by an extension of the work of Sobocinski et al.[13] as outlined below.

The influence of various concentrations of galactose and mannose on the Dische-Shettles CyR3 reaction was determined by setting up an 8 x 6 matrix consisting of all possible combinations of fucose concentrations of 0, 2.5, 5.0, 7.5, 10.0, 15.0, 20.0, and 25.0 mg/dl and 0, 75.0, 100.0, 150.0, 200.0, and 250.0 mg/dl of equimolar galactose-mannose solutions.

Similar matrices were set up to evaluate the influence of hexosamines (as N-acetylglucosamine) or sialic acid (as N-acetylneuraminic acid) on the apparent concentration of fucose as given by the CyR3 reaction.

To quantify the protein-bound neutral hexoses (as galactose and mannose), nonprotein materials were eliminated by precipitation of 0.05 ml serum with 5.0 ml 95 percent ethanol. The precipitated proteins were separated by centrifugation at 12,000 rpm (17,300 x g) for 10 min at 15°C in a Sorvall Model RC2 refrigerated centrifuge equipped with an SS-34 angular head. The supernate was carefully decanted;

the precipitate was washed with an additional 5.0 ml ethanol, and the centrifugation and decantation repeated. The packed, drained precipitate was dissolved by addition of 1.0 ml 0.1 N NaOH solution. This solution was transferred to the sample cups of a Technicon AutoAnalyzer (Technicon Corporation, Tarrytown, New York). The analyses were completed from this point by the automated column chromatographic method of Armstrong[2] as adapted by Sobocinski et al.[14] to sample individual serum preparations rather than column eluate.

All the analytical procedures were carried out in duplicate.

The results of the clinical studies were tabulated and plotted in terms of milligrams protein-bound neutral hexoses per 100 mg biuret protein and micrograms L-fucose per milligram protein to offset the effect on the concentrations of the respective carbohydrates occasioned by the relative or absolute hypoproteinemia found in a majority of the patients.

III. RESULTS

The substantial influence of the neutral hexoses galactose and mannose on the estimation of protein-bound fucose by the Dische-Shettles CyR3 reaction is illustrated in Figure 1.

The work of Sobocinski et al.[13] was confirmed in that each of the family of parallel lines generated by increasing amounts of neutral hexoses in the reaction mixture was displaced by a distance proportionate to the added concentration of galactose-mannose throughout the ranges tested. Therefore, a correction factor similar to theirs could be derived.

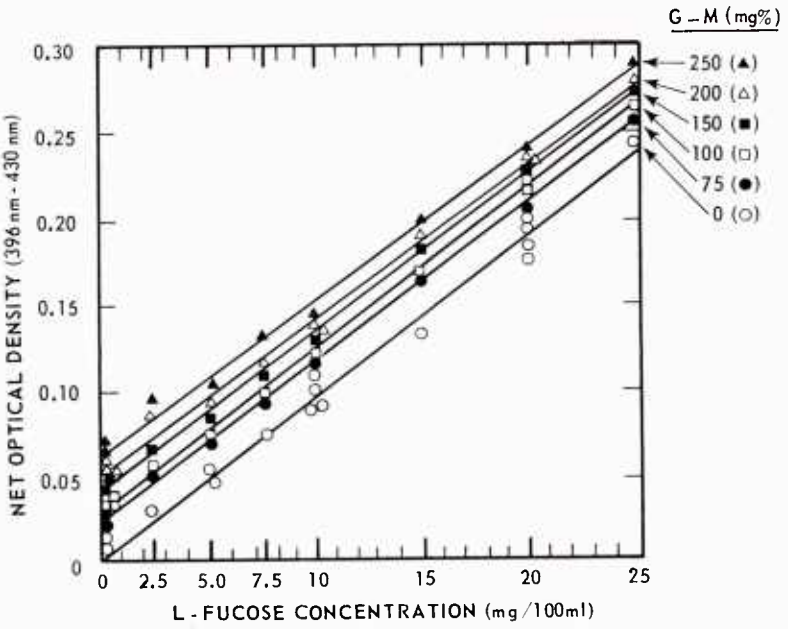

Figure 1. Influence of various concentrations of galactose and mannose (G-M) on the apparent concentration of L-fucose as estimated by the Dische-Shettles CyR3 reaction. Each data point represents the mean of duplicate determinations. Regression lines were fitted by the method of least squares.

In our hands, this correction was expressed by the equation:

$$F(C) = F(R) - 0.021(NH) + 0.758$$

where

F(C) = corrected fucose, mg/dl,

F(R) = raw fucose, mg/dl, and

(NH) = neutral hexoses, mg/dl.

Neither hexosamine nor sialic acid exerted any influence on the apparent fucose concentration by the CyR3 reaction when tested through the physiological and pathological ranges.

None of the other tested carbohydrates, fucose, hexosamine, or sialic acid, exerted any remarkable effect on the apparent concentration of neutral hexoses.

That it is valid to compute the carbohydrate to protein ratios utilizing the standard biuret procedure on whole serum is shown by Figure 2. Thus, the protein content of the ethanol precipitate employed to estimate the concentration of protein-bound carbohydrates is not significantly different from that obtained on whole serum.

Table I summarizes numerically, and Figures 3 and 4 present graphically, the distribution of serum protein-bound neutral hexose and corrected fucose to protein ratios found in the 109 patients with primary diagnoses of malignant neoplasia.

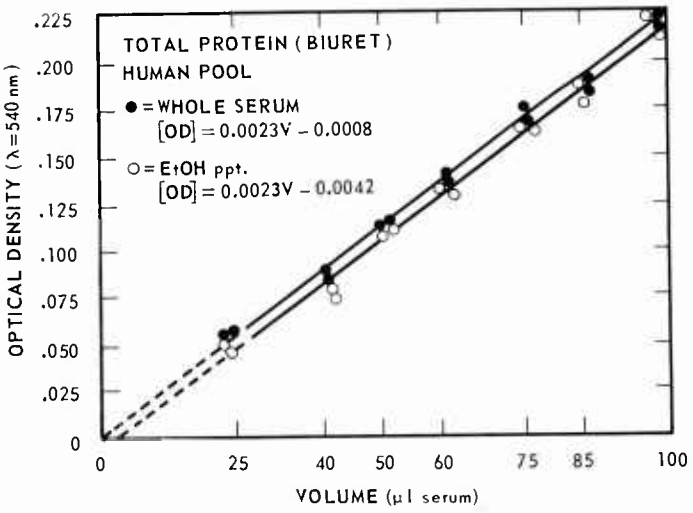

Figure 2. Total protein (biuret) as determined in whole serum (•) or the washed ethanol precipitate (o) from which the bound carbohydrates are determined. Each data point represents the mean of duplicate determinations. Regression lines were fitted by the method of least squares.

Table I. Summary of Results in 109 Patients with Primary Diagnoses of Malignant Neoplasia

Category	Number	Number and percent with elevated ratios of:		
		Neutral hexoses/ protein	L-fucose/ protein	Both parameters
Untreated tumors*				
Disseminated	72	60 (83.3%)	68 (94.4%)	59 (81.9%)
Localized	11	2 (18.2%)	6 (54.5%)	2 (18.2%)
Under treatment or observation†				
Responding poorly	7	7 (100.0%)	7 (100.0%)	7 (100.0%)
Clinically quiescent	10	2 (20.0%)	2 (20.0%)	1 (10.0%)
No tumor burden	9	1 (11.1%)	0	0

* Graphically represented in Figure 3
† Graphically represented in Figure 4

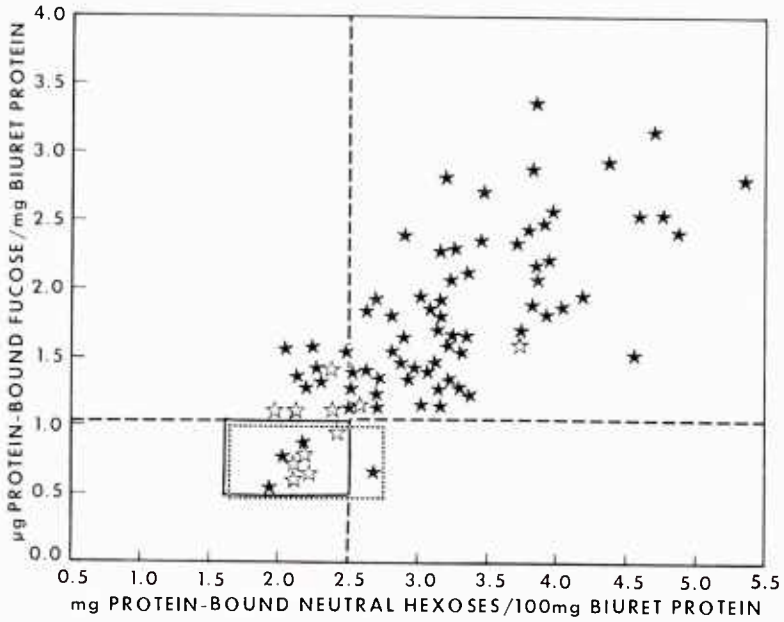

Figure 3. Distribution of pretreatment serum protein-bound fucose to protein and neutral hexose to protein ratios in 83 patients with primary diagnoses of malignant neoplasia who were determined to have had disseminated (★) or localized (☆) disease. The rectangular area limited by a solid line encompasses the 107 normal control values. The broken rectangle encloses the values of 39 normal, uncomplicated pregnancies.

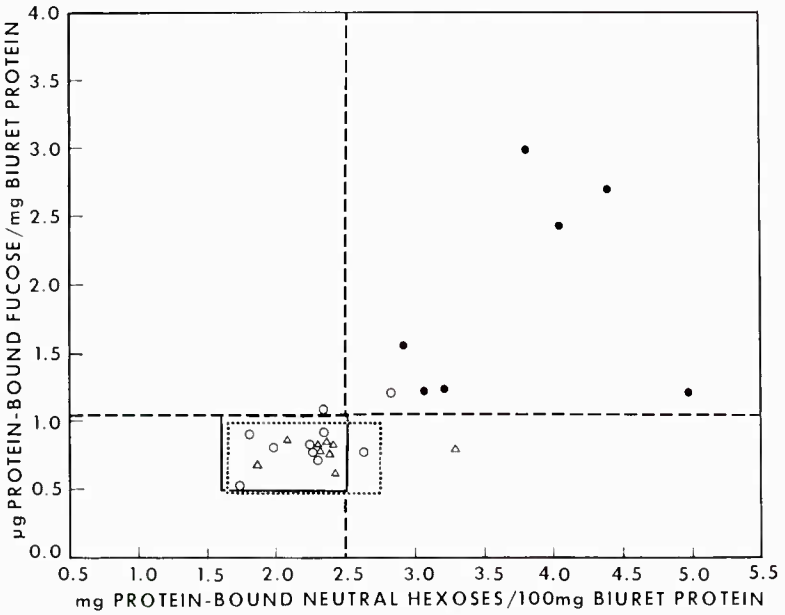

Figure 4. Distribution of serum protein-bound fucose to protein and neutral hexose to protein ratios in 26 patients who had been under treatment or observation for varying periods of time and were without tumor burden (△), clinically quiescent (o), or responding unsatisfactorily to therapy (•). The rectangular area limited by a solid line encompasses the 107 normal control values. The broken rectangle encloses the values of 39 normal, uncomplicated pregnancies.

IV. DISCUSSION

Utilization of the correction factor derived herein to eliminate the influence of the neutral hexoses galactose and mannose on the Dische-Shettles CyR3 reaction appears to have several advantages.

Thus, the protein-bound fucose concentrations in the normal controls are lowered to a range comparable to that one would expect from back calculating and summing the fucose content of the individual proteins,[15] yields values comparable to the specific enzymic method,[13] and narrows and normalizes the distribution (Figures 3 and 4, solid rectangle).

Of more importance, initial clinical application of the revised methodology to test the utility of fucose and neutral hexose to protein ratios appears to justify further investigation toward eventual definition of the pathognomonic significance of the response of the protein-bound carbohydrates in neoplastic diseases.

Thus, when one considers those cancer patients from whom serum specimens were obtained before any definitive therapy had been undertaken on their current admission, and who were later clinically or surgically assessed to have had varying degrees of disseminated disease (Table I, Figure 3, solid stars), 68 of the 72 cases (94.4 percent) had elevated fucose to protein ratios.

There was no common denominator in the four cases of disseminated disease which did not exhibit an abnormal fucose except a marked fibroplasia intimately associated with both the primary lesion and the metastatic foci. These cases were two bronchogenic carcinomas (one a recurrence in the bronchial stump 2 years postlobectomy), an adenocarcinoma of the ascending colon, and a large (20 x 10 cm) moderately well differentiated adenocarcinomatous pelvic mass. Involvement of regional lymph nodes was the only demonstrable evidence of dissemination of disease in all but the pelvic mass, which presented massive omental metastases. It should be noted, however, that serum specimens taken from the latter patient 1 and 3 months later were elevated in both protein-bound fucose and neutral hexose to protein ratios.

The above discussion leads to some rather compelling speculation when applied to the few (11) cases where no evidence of metastasis was found (Table I, Figure 3, open stars). If one assumes that an elevation in fucose to protein ratio is indicative of some degree of dissemination of the tumor, one is forced to conclude that the six

patients with abnormal fucose to protein ratios, and especially the two in whom the neutral hexose to protein ratio was also elevated, may harbor an occult metastatic lesion. The validity of such speculation is enhanced when one considers the empirical nature of clinical and surgical assessment of localized versus disseminated disease. Thus, while a finding of lymph node or other involvement is positive evidence of metastasis, the failure to demonstrate such involvement is not conclusive.

A similar argument leads directly to a comparison of the results from patients who had been under treatment (radiotherapy, chemotherapy, or combination), or who had had no evidence of tumor burden after definitive surgery, for varying periods of time before entering the present study.

Eight of the ten patients whose tumors were clinically quiescent (Figure 4, open circles), and all of those (9) whose tumors had been successfully excised (Figure 4, open triangles), were within the normal fucose to protein range. By contrast, all seven cases (Figure 4, closed circles) who were not responding satisfactorily to their therapy had elevated values of both fucose and neutral hexoses. One must surmise, then, that the two patients who were assessed to have stable disease, but whose fucose to protein ratios were abnormal, were not under as effective control as their clinical evaluation indicated.

While the results in this series of patients with established diagnoses of malignant neoplasia indicate excellent correlation for presurgical estimation of tumor extension or activity and postsurgical evaluation of therapeutic efficacy, the parameters reported herein are not by themselves sufficient for differential diagnostic application.

Thus, in the 61 patients hospitalized for a variety of nonmalignant disease states, nearly one-third had elevated fucose to protein ratios, and an equal number (not the same individuals) exhibited abnormal neutral hexose to protein ratios.

The patients categorized as "false positives" included persons with such varied conditions as active pulmonary tuberculosis, clinical hyperthyroidism, acute ileitis and ulcerative colitis, massive intra-abdominal injury with sepsis, two cases of ruptured berry aneurism, one large pulmonary abscess with empyema, and one patient with terminal uremia.

The nine cases of acute ileitis or ulcerative colitis presented an interesting picture in that, while the fucose to protein and neutral hexose to protein ratios were both elevated on admission, both carbohydrates returned rapidly to the normal range with treatment. Similarly, while several clinically hyperthyroid persons were normal in this test system, one 60-year-old male was elevated when hyperthyroid and normal when euthyroid.

At autopsy, the pulmonary abscess patient (an 87-year-old female whose concurrent diagnoses included congestive heart failure and diabetes) demonstrated tumorlets in the periphery of the abscess cavity. This finding raises the unanswerable question of whether the patient's primary problem was a pulmonary neoplasm of which the tumorlets were the only visible residua, or whether the tumorlets themselves could have caused the elevated carbohydrate to protein ratios.

Such cases point to the uncertainty involved in relegating abnormal values in patients with diagnoses of nonmalignant disease to the category of "false positives".

That is, such classification is done by the very clinical means the procedures under development and testing are intended to complement.

Indeed, six of the patients included in the neoplasia group (Figure 3) were individuals who had been admitted to the hospital with diagnoses other than that of malignancy, but in whom subsequent work-up demonstrated either an occult tumor or concurrent metastatic disease not associated with the chief complaint for which they had been admitted.

Only careful and extended follow-up on a large number of patients can resolve such dilemmas and establish objective criteria to signal the presence of concurrent, underlying processes.

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13. ABSTRACT

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